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Original Article

Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case–control study

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ABSTRACT

Objective: To investigate demography and clinic and polysomnographic characteristics in Chinese rapid eye movement (REM) sleep behavior disorder (RBD) patients across onset ages.
Methods: Ninety consecutive patients fulfilling the criteria for RBD were recruited for study in our sleep center. Patients were separated into early- and late-onset groups according to age when symptoms began (⩽50 and >50 years, respectively). Ninety age- and gender-matched healthy subjects served as controls. All subjects were interviewed for their clinical history, completed an RBD questionnaire, and underwent an overnight video polysomnography assessment. Demographics, comorbidities, scores on the RBD questionnaire, sleep architecture, and EMG activity were compared between the patients and controls and between the early- and late-onset groups.
Results: Of all RBD patients, 63 were male, and mean age of RBD onset was 54.3 ± 15.7 years. In 25 patients (28%), RBD was secondary and associated with neurodegenerative disease, narcolepsy or antidepressant use. Twenty-three patients (26%) had early-onset RBD and 67 (74%) were in the late-onset group. RBD patients had significantly more comorbidities, dreams and dream-enacting behaviors, and poorer sleep quality than did controls. The early-onset group had a high proportion of females (48%) and an increased proportion of cases associated with narcolepsy. The early-onset group also had fewer movements, lower EMG activity during REM sleep, and better sleep quality when compared to the late-onset group. EMG activity was positively correlated with age of onset. The mean follow-up time was 1.57 ± 0.82 years, and four patients in the late-onset group were subsequently diagnosed with neurodegenerative diseases.
Conclusions: Stratifying patients into early and late-onset RBD revealed different characteristics from those previously described as typical for RBD. EMG activity during REM sleep was positively correlated with age of onset. We suggest that it will be valuable to explore the relationship between age of onset conversion and neurodegenerative diseases.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of normal muscle atonia during REM sleep. It is associated with dream-enacting behaviors such as talking, yelling, punching, kicking or jumping out of bed that disrupt sleep and may result in severe injuries for the patient or the bed partner [1,2]. RBD was first described as a medical disorder in humans in 1986 [3], and it was observed predominantly in elderly men [4]. A new study reported that the prevalence of idiopathic RBD was about 1.15% in the Korean elderly population [5]. RBD is categorized as idiopathic or secondary according to associations with other functional or structural disorders of the nervous system. A strong relationship between RBD and neurodegenerative diseases including Parkinson disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) has been described. It also has been linked with narcolepsy, cerebrovascular disease and medication (particularly antidepressants).

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Current evidence indicates that a high proportion of patients (48–75%) has secondary RBD [2,6,7]. Furthermore, idiopathic RBD cases frequently develop a neurodegenerative disease within 5–20 years [8]. Recently, the term 'idiopathic' RBD has been questioned, with the suggestion that it should be replaced by 'cryptogenic' RBD [9].

Since RBD patients have the potential injuries to themselves or their bed partners and have the possibility of developing neurodegenerative disease, it is an important clinical disease. Several case series have described the demographic and clinical features of RBD. However, there are few studies of RBD in Chinese patients [10–12] and it has not received adequate attention in the Chinese community. Moreover, recent studies report different demographic and clinical features of RBD according to onset age [8,13,14]. Studies distinguishing age of onset have reported a higher proportion of females, higher rates of psychopathology, a potential role for autoimmune dysfunction, and a lower rate of neurodegenerative disease in early-onset patients [8,13,14]. These studies suggest that early-onset RBD may have a significantly different clinical profile than late-onset RBD, which is linked more closely to elderly men and a high probability for neurodegenerative diseases [8,13]. Therefore our aim in this study was to compare the clinical characteristics of Chinese RBD patients with healthy controls to determine potential differences between 'early-onset' and 'late-onset' RBD.

2. Methods

2.1. Subjects

The present study was conducted with a prospective design. Ninety consecutive patients fulfilling the criteria for RBD were recruited between November 2009 and July 2012 at the Sleep Medicine Center of West China Hospital. RBD was diagnosed according to the International classification of sleep disorders (2nd edition) (ICSD-2) criteria [1]. Control subjects were recruited through newspaper advertisement. They were 90 age- and gender-matched healthy volunteers without history of abnormal behaviors during sleep, without any neurological disorder (e.g. stroke, brain trauma, neurodegenerative disease and narcolepsy), and who were not receiving any central nervous system active medication. The study was approved by the hospital ethics committee and all subjects gave written informed consent before their participation.

All subjects were required to complete an RBD questionnaire (RBDQ-HK) and underwent overnight video-polysomnography (PSG) assessment. Patients were interviewed to obtain age and gender, and clinical details including duration of disease, comorbidity, and the use of medications or substances. Associated neurological disorders were diagnosed by consulting neurologists. RBD was classified as secondary in cases of comorbid neurological disorder (e.g. narcolepsy, neurodegenerative disease), or when it was associated with medication use (e.g. antidepressant). All other cases were categorized as idiopathic. Patients were defined as early- or late-onset according to the onset age. Patients aged $\leqslant$50 years were classified as early-onset RBD and those aged >50 years were classified as late-onset RBD.

2.2. RBDQ-HK questionnaire

All participants and their bed partners were asked to complete a 13-question RBD questionnaire (RBDQ-HK) with items related to the subjects' dream content and dream-enacting behaviors [15]. This questionnaire has established validity and reliability for assessing the clinical symptoms and severity of RBD [15]. Each questionnaire item was scored according to the frequency of occurrence of relevant dream- and behavior-related factors during sleep. Factor 1 (dream-related) characterized the dreams and nightmares that led to nocturnal behaviors and disrupted sleep; factor 2 (behavioral) assessed the sleep-related behavior including vocalization, abnormal motor activities, and injuries to self and/or bed partners. Questionnaire scoring followed previous work and used a cut-off for total score (range, 0–100) at 18/19 and a cut-off for factor 2 (range, 0–70) at 7/8 [15].

2.3. Polysomnography

All subjects underwent one full-night of PSG assessment synchronized with video recording. Overnight PSG consisted of continuous recordings from electroencephalography (EEG) (F4–M1, C4–M1, O2–M1, F3–M2, C3–M2, O1–M2), electro-oculography (EOG) (ROC–M1, LOC–M2), submental electromyography (EMG), right and left anterior tibialis surface EMG, electrocardiography (ECG), nasal and oral airflow, thoracic and abdominal respiratory movements, oxygen saturation, and body position. Audiovisual recordings were simultaneously performed. Sleep stages and REM sleep without atonia were scored according to the criteria described in the American Academy of Sleep Medicine (AASM) manual [16].

The following sleep variables were obtained and analyzed: sleep latency (SL), REM sleep latency, sleep efficiency (SE), total sleep time (TST), percentage spent in stage N1, N2, N3 and REM sleep, number of REM sleep periods, wake after sleep onset (WASO), apnea–hypopnea index (AHI), and periodic leg movement index (PLMI).

2.4. Analysis of EMG activity

Quantification of tonic and phasic EMG activity during REM sleep was performed manually in each participant. Increases in EMG tone due to arousals from respiratory events and artifacts (e.g. snoring) were excluded from analysis. Tonic and phasic EMG activity were scored manually according to the criteria of the 2007 AASM manual [16]. Tonic EMG activity was scored from the EMG recording in 30 s epochs. An epoch was scored as 'tonic' when the sustained EMG activity was present in more than 50% of the duration of the epoch with amplitude greater than the minimum amplitude in non-REM. Phasic EMG activity was scored from a 30 s epoch of REM sleep recording which was divided into 3 s mini-epochs requiring that at least five (50%) of the mini-epochs contain bursts of EMG activity lasting between 0.1 and 5.0 s with amplitude four times the background EMG activity. We calculated separately the percentage of 30 s epochs with tonic and phasic EMG activity. Total EMG activity was calculated as the percentage of phasic EMG activity plus the percentage of tonic EMG activity [17].

2.5. Follow-up visit

All of the patients included in this study were assessed in a follow-up visit through October 8, 2012. The main purpose of the follow-up was to determine potential conversion from idiopathic RBD to neurodegenerative disease.

2.6. Statistical analysis

SPSS 17.0 was used for all statistical analyses. Data are presented as mean ± standard deviations or frequencies (percentages). The qualitative data were analyzed using chi-square or Fisher's exact test as appropriate. Comparison between two groups on continuous variables was conducted using Student's *t*-test. If the data had an abnormal distribution, non-parametric tests (Mann–Whitney test) were performed. Associations between variables were

assessed using Spearman's correlation procedures if the data were not normally distributed. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics are presented in Table 1. We identified 90 patients who met ICSD-2 criteria for RBD. Ninety age- and sex-matched healthy volunteers were recruited to serve as the normal controls. Sixty-three (70%) of the patients were male. The mean age of RBD onset was 54.3 ± 15.7 years (range, 13–79) and the mean age of diagnosis was 59.1 ± 15.5 years (range, 18–84). There was no significant difference in the mean age between patients and controls (57.5 ± 14.2 years). Patients with RBD were divided into two groups according to RBD onset age: early-onset (⩽50 years) and late-onset (>50 years) RBD. There were 23 early-onset patients (26%) and 67 late-onset patients (74%). The early-onset group contained an almost equal proportion of males (52%) and females (48%), but males formed the highest percentage (76%) of late-onset patients. The mean age at diagnosis of RBD for the early-onset RBD was 38.3 ± 13.6 years and the mean age of the late-onset RBD group was 66.2 ± 7.9 years. RBD duration was not significantly different between the early-onset RBD and late-onset RBD groups.

Sixty-five cases (72%) were categorized as idiopathic and the remaining 25 patients (28%) were categorized as having secondary RBD. The idiopathic form of RBD was predominant in late-onset RBD (78%), and made up less of a percentage (57%) of early-onset RBD. The secondary form was associated with neurodegenerative disease in 14 patients (11 PD, two MSA, and one DLB), with narcolepsy in four patients and with antidepressant-taking in seven patients (one psychosis, six depressions). Most of the neurodegenerative diseases were coincident with late-onset RBD. Eight patients with daytime sleepiness underwent multiple sleep latency test after the PSG assessment. The mean initial sleep latency of these patients was <8 min. According to ICSD-2 criteria, four patients fulfilled the diagnostic criteria for narcolepsy (two with cataplexy) and all were in the early-onset group. Four other patients had obstructive sleep apnea with daytime sleepiness. The control group was healthier as indicated by the absence of mental and neurological disorders. Patients with RBD had significantly higher AHI and PLMI than controls ($P < 0.05$) with no significant difference between the early- and late-onset groups. We confirmed that these patients with higher AHI had movements and increased tonic and phasic EMG activity during REM sleep.

3.2. RBDQ-HK

The frequency of dreams and dream-enacting abnormal behaviors in RBD patients over the past one-year period was examined (Fig. 1). Eighty-two patients (91%) reported dreams more than three times per week. The content of dreams consisted of nightmares, emotional dreams, violent dreams, and frightening dreams. During this period, 94% of patients had nightmares, 80% of patients had violent and frightening dreams, 99% of patients had sleep talking and 92% of patients had shouting during sleep. Eighty-six patients (96%) had obvious sleep-related movements consisting of arm waving, punching and kicking. Sixty-seven patients (74%) had falling from bed and 68 patients (76%) had sleep-related injuries. Forty-nine patients (54%) reported sleep disturbance associated with vivid dreams and behaviors during sleep.

RBD patients had a significantly higher RBDQ score than controls ($P < 0.01$). There were no significant differences between early- and late-onset RBD patients on the RBDQ for the factor 1 score and total score. Nonetheless, the factor 2 score was higher in the late-onset group than in early-onset patients ($P < 0.05$), indicating that the late-onset group had higher severity for dream-enactment behaviors (Table 1).

3.3. Polysomnographic parameters

The polysomnographic findings of all RBD patients and controls are presented in Table 2. The PSG showed that patients with RBD had poorer sleep quality as indicated by significantly higher amounts of stage N1 sleep, lower amounts of stage N3 sleep, longer WASO time, higher AHI and PLMI, and worse sleep efficiency when compared with controls ($P < 0.05$). None of the other sleep parameters differed between RBD patients and controls. Early-onset RBD patients had longer total sleep time, higher sleep efficiency, lower

Table 1
Demographic and clinical characteristics and questionnaire scores for RBD patients and controls.

Demographic and clinical characteristics	All RBD vs controls			Early- vs late-onset RBD		
	All RBD ($n = 90$)	Controls ($n = 90$)	P-value	Early-onset RBD ($n = 23$)	Late-onset RBD ($n = 67$)	P-value
Male, n (%)	63 (70%)	63 (70%)	1.000	12 (52%)	51 (76%)	0.031
Age at onset (years)[a]	54.3 ± 15.7	N/A	N/A	32.3 ± 12.4	61.8 ± 7.3	0.000
Age at diagnosis (years)[a]	59.1 ± 15.5	57.5 ± 14.2	0.328	38.3 ± 13.6	66.2 ± 7.9	0.000
Duration of disease (years)[a]	4.8 ± 4.2	N/A	N/A	6.0 ± 5.6	4.4 ± 3.6	0.357
Idiopathic RBD, n (%)	65 (72%)	N/A	N/A	13 (57%)	52 (78%)	0.051
Secondary RBD, n (%)	25 (28%)	N/A	N/A	10 (43%)	15 (22%)	0.051
Neurodegenerative disease, n (%)	14 (16%)	N/A	N/A	2 (9%)	12 (18%)	0.472
Parkinson's disease, n (%)	11 (12%)	N/A	N/A	1 (4%)	10 (15%)	0.333
Multiple system atrophy, n (%)	2 (2%)	N/A	N/A	1 (4%)	1 (1%)	1.000
Dementia with Lewy bodies, n (%)	1 (1%)	N/A	N/A	0	1 (1%)	1.000
Narcolepsy, n (%)	4 (4%)	N/A	N/A	4 (17%)	0	0.003
Antidepressant use, n (%)	7 (8%)	N/A	N/A	4 (17%)	3 (5%)	0.123
AHI > 10/h, n (%)	14 (16%)	5 (6%)	0.029	2 (9%)	12 (18%)	0.472
PLMI > 15/h, n (%)	23 (26%)	11 (12%)	0.022	2 (9%)	21 (31%)	0.061
RBDQ-HK[a]						
Factor 1 score	16.9 ± 5.5	7.8 ± 2.8	0	18.0 ± 6.5	16.4 ± 5.1	0.419
Factor 2 score	36.0 ± 11.0	1.6 ± 2.9	0	30.9 ± 9.0	37.9 ± 11.2	0.025
Total score	52.8 ± 12.6	9.4 ± 4.6	0	48.9 ± 10.4	54.3 ± 13.1	0.190

RBD, rapid eye movement sleep behavior disorder; AHI, apnea–hypopnea index; PLMI, periodic limb movement index; RBDQ-HK, RBD questionnaire – Hong Kong; N/A, not applicable.
[a] Mean ± SD.

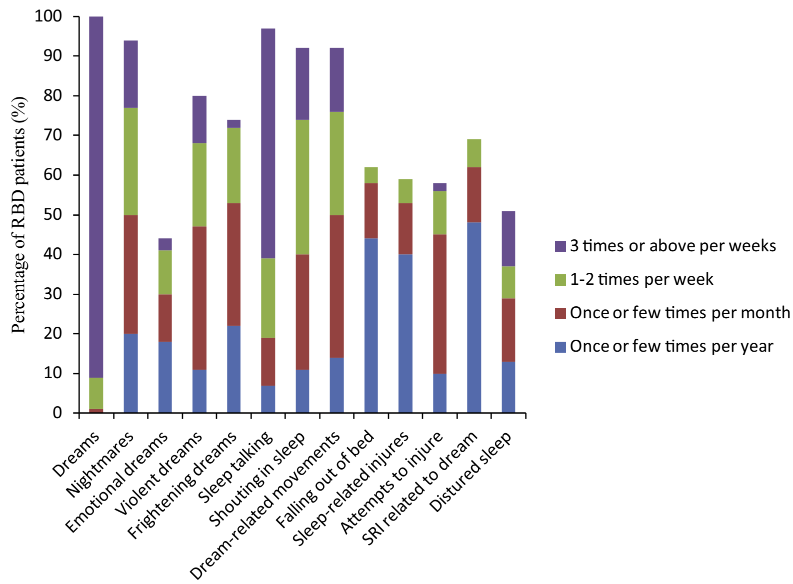

Fig. 1. Frequency of dreams and dream-enacting behaviors in RBD patients. SRI, sleep-related injuries.

Table 2
Sleep architecture and EMG variables in RBD patients and controls.

Sleep variables	All RBD vs controls			Early- vs late-onset RBD		
	All RBD (n = 90)	Controls (n = 90)	P-value	Early-onset RBD (n = 23)	Late-onset RBD (n = 67)	P-value
Sleep latency (min)	20.9 ± 23.3	14.2 ± 7.0	0.518	15.5 ± 20.0	23.0 ± 24.3	0.125
REM sleep latency (min)	142.2 ± 96.3	108.8 ± 56.2	0.064	144.9 ± 133.0	141.2 ± 80.5	0.416
Sleep efficiency (%)	73.6 ± 15.8	80.5 ± 11.3	0.028	84.2 ± 17.1	69.7 ± 13.6	0.000
Total sleep time (min)	388.1 ± 82.8	412.4 ± 56.8	0.121	424.0 ± 92.9	374.7 ± 75.6	0.018
Stage 1 (%)	17.3 ± 12.9	10.6 ± 5.4	0.036	12.0 ± 11.3	19.2 ± 12.9	0.043
Stage 2 (%)	52.9 ± 16.2	54.2 ± 12.7	0.960	56.1 ± 12.7	51.7 ± 17.3	0.307
Stage 3 (%)	10.5 ± 7.6	16.5 ± 9.8	0.001	12.3 ± 6.7	9.9 ± 7.8	0.210
Stage REM sleep (%)	19.3 ± 9.1	18.6 ± 7.7	0.749	19.6 ± 8.8	19.1 ± 9.3	0.556
WASO (min)	121.6 ± 85.7	91.2 ± 61.5	0.035	70.7 ± 105.4	140.5 ± 69.5	0.000
REM sleep periods (n)	5.3 ± 2.9	6.3 ± 3.0	0.031	6.1 ± 2.6	4.9 ± 2.9	0.053
3 s REM mini-epochs (n)	1529.8 ± 835.7	1558.6 ± 655.2	0.615	1711.8 ± 842.2	1462.6 ± 832.3	0.143
Phasic EMG activity (%)	9.4 ± 9.8	0.5 ± 0.9	0.000	3.2 ± 3.5	11.7 ± 10.4	0.000
Tonic EMG activity (%)	20.6 ± 16.9	1.4 ± 2.9	0.000	13.9 ± 14.2	23.0 ± 17.4	0.034
Phasic + tonic EMG activity (%)	30.0 ± 19.7	1.9 ± 2.8	0.000	17.0 ± 15.8	34.8 ± 19.0	0.001

EMG, electromyography; RBD, rapid eye movement (REM) sleep behavior disorder; PLMI, periodic limb movement index; WASO, wake after sleep onset.
Values are mean ± SD.

amounts of stage N1 sleep, and shorter WASO time than did late-onset patients ($P < 0.05$). No differences were found for any of the other sleep variables in comparisons between early- and late-onset RBD patients.

3.4. Analysis of EMG activity

We manually analyzed 3 s mini-epochs of REM sleep (Table 2). There was no significant difference in REM mini-epochs between patients with RBD and controls, or between early- and late-onset RBD. The mean phasic, tonic and total EMG activities were significantly higher in patients with RBD than in controls ($P < 0.01$), and the late-onset RBD patients showed higher phasic, tonic and total EMG activities than the early-onset group ($P < 0.01$). Phasic EMG activity was positively correlated with age of onset ($r = 0.427$, $P < 0.01$), as were tonic EMG activity ($r = 0.265$, $P < 0.05$) and total EMG activity ($r = 0.296$, $P < 0.05$).

3.5. Follow-up visit

The mean follow-up time was 1.57 ± 0.82 years (range, 0.2–3). Three patients developed PD after a history of more than 10 years (range, 11–16) of RBD. One patient was diagnosed with frontal–temporal dementia after a 3.5-year history of RBD and atrophy of left temporal lobe. All of these patients were in the late-onset group.

4. Discussion

4.1. Demographic and clinical characteristics

RBD usually emerges after the age of 50 years. In our study, the mean age of onset was 54 years, similar to the 52 years reported by Schenck [2]. Moreover, only 26% of patients were aged <50 years. Generally, RBD is thought to occur predominantly in males and this sex difference has been considered a hallmark of RBD. Indeed, more than 80% of patients with RBD were male in two large studies [2,6] which is in line with the 70% of the total patients with RBD being male in the current study and with two previous studies with Chinese patients with RBD in Taiwan (65%) and Hong Kong (75%) [11,12]. The reason for male predominance is still unknown. It has been suggested that sex hormone abnormalities may result in more aggressive and violent behaviors in men [18], but recent

studies have not verified this possibility [19,20]. Recent studies have found more gender parity in early-onset RBD [8,13,17] in line with the 52% males we found in our early-onset group. One possible reason for fewer males with early-onset RBD might be the fact that antidepressant-related cases more typically involve females. In this study, four cases (17%) related to antidepressants in younger patients were female. Teman et al. also reported a larger percentage of females in younger RBD patients and suggested that the difference might be due to the increased prevalence of depression in women [14].

There is an increasingly recognized association between secondary RBD and neurological disease, and previous studies have reported that more than 50% of RBD patients have neurological disease [2,6,21]. In our study, 18 patients (20%) also had neurodegenerative disease or narcolepsy, thereby supporting the hypothesis that RBD could be the first symptom of neurodegenerative disease. Indeed, for idiopathic RBD, it has been estimated that 5-year risk of neurodegenerative disease is 17.7%, the 10-year risk 40.6% and the 12-year risk 52.4% [22]. Therefore, neurological follow-up of these patients with idiopathic RBD is necessary.

Our data showed that 57% early-onset patients had idiopathic RBD. The factors most frequently associated with early-onset RBD were narcolepsy (17%) and antidepressant use (17%). Narcolepsy is highly comorbid with RBD. Narcolepsy was present in 38% of early-onset RBD in one large study [13], but there is no definitive hypothesis about the pathophysiological mechanism linking RBD with narcolepsy. Antidepressant was another important risk factor associated with RBD. RBD was usually induced by tricyclic antidepressants and selective serotonin reuptake inhibitors. In our study, seven patients with psychiatric disease (8%) had typical symptoms of RBD after taking antidepressants. This proportion is lower than the 25–33% found in previous studies [6,10]. We speculate that fewer psychiatric populations visit our sleep center because it is independent of the psychiatric department in our hospital. The mechanism that links antidepressant use and RBD was postulated that the enhancement of REM-related EMG activity by antidepressant [23]. However, this hypothesis was not fully supported by a recent study, which found that REM-related muscle atonia was not completely restored after withdrawal of the antidepressants [24]. Furthermore, a study from the same laboratory revealed that depression itself was a risk factor in predicting PD in idiopathic RBD patients [25]. In a case–control study, the etiology of RBD in psychiatric populations was found to be complex, related to individual predisposition, depressive illness, and antidepressants [26].

Sixteen percent of patients in this study had AHI >10/h, which was higher than in our controls, but was far less than the 60.6% of RBD patients that had AHI >10/h reported in a recent study [27]. Surprisingly, this recent study showed that RBD patients with OSA had lesser severity of sleep apnea than OSA controls, and suggested that excessive EMG activity might protect patients against severe OSA [27].

Periodic limb movement syndrome (PLMS) is reported in about 50–70% of RBD patients [2,6,12]. In our study the prevalence of PLMS (PLMI >15/h) (26%) was less than that in previous reports. Comparing late- with early-onset RBD, there was a propensity for a PLMS in elderly patients with RBD. This was consistent with a report that 20% of normal subjects aged >65 years had PLMI >20/h [28].

4.2. Dream and dream-enacting behavior

Patients with RBD usually have vivid memories about dreams. Most of their dreams are negative, violent or frightening. In the current study, patients with RBD had significantly more dreams and movements during sleep than controls. Few healthy people had talking or shouting; none reported falling out of bed or injury from behavior during sleep. By comparison, 96% of RBD patients had sleep-related movements and 74% of patients reported falling from bed. Sleep-related injury is a typical feature of RBD and the primary reason for doctor visits. The prevalence of sleep-related injury in our studies (76%) was similar to that in previous studies (66–79%) [2,6]. However, it has been reported that most motor events during REM sleep in RBD were minor and that violent episodes represented only a small fraction of incidents [29]. We also found that male patients had more limb movements and more falling out of bed than did female patients (7.4 ± 2.2 vs 5.0 ± 2.9, $P = 0.001$; 3.8 ± 2.2 vs 2.3 ± 2.4, $P = 0.015$). This may be an important factor for the male predominant prevalence in idiopathic RBD because the less aggressive and violent behaviors in female patients could lead to less seeking of medical attention. In this regard, the sex differences in RBD prevalence and symptom severity should be further examined in the general population. There were also more sleep-related behaviors in late-onset than early-onset RBD. Ju et al. also reported that only a minority of cases showed violent behaviors in early-onset RBD [8]. Therefore, a small proportion of males among early-onset RBD patients may present less dramatic nocturnal behaviors.

4.3. Polysomnography

Our findings showed that RBD patients had a lower amount of slow wave sleep (SWS) and had poorer sleep quality than controls. By comparison, other studies have reported a higher percentage of SWS in RBD patients [2,6,30,31]. Interestingly, it has been suggested that EEG slowing may represent a very early sign of cortical dysfunction and cognitive deficit [32,33]. Others have reported no difference in SWS between RBD patients and healthy controls [33,34]. However, the PSG parameters in the current study showed that late-onset patients had shorter total sleep time and poorer sleep quality than did early-onset patients. There are quantitative and qualitative changes in sleep with age, especially decreased nocturnal sleep duration and with SWS being the stage most affected [35]. Moreover, sleep disturbance occurs frequently in neurodegenerative disease. So we speculate that the poorer sleep quality in the late-onset group is related to movements during sleep, age, and potentially to neurodegenerative disorders.

4.4. Analysis of EMG activity

In the ICSD-2, the criteria for RBD diagnosis do not provide a quantitative mode for evaluating ‘excessive EMG activity’. Additionally, the assessment of REM sleep without atonia (RWA) is based on the scorer’s subjective qualitative impression. Unfortunately, the ICSD-2 does not specify common quantitative scoring rules and cut-off values in EMG activity for RBD diagnosis. Recently, Frauscher et al. reported two studies about qualitative to quantitative assessment of EMG activity during REM sleep [36,37]. They suggested a cut-off for RBD diagnosis of 16.3% for phasic EMG activity and 9.6% for tonic EMG activity. The tonic EMG activity of our RBD patients was much higher than 9.6%, but phasic EMG activity was lower than the cut-off. A possible reason for this difference was that our criterion of quantitative scoring for phasic EMG activity was different from previous studies. According to the AASM guidelines [16], phasic EMG activity requires that at least five (50%) of the mini-epochs contain EMG activity lasting between 0.1 and 5.0 s with amplitude more than four times the background EMG activity. However, there was no requirement of at least five mini-epochs for scoring phasic EMG activity in previous studies. Interestingly, we found that the results of tonic and phasic EMG activity were very similar to a study by Zhang et al. in Hong Kong Chinese (tonic, 20.6 ± 16.9 vs 24.3 ± 23.4; phasic,

9.7 ± 7.8 vs 9.4 ± 6.4) [17]. The scoring and calculation rules of EMG activity in the Hong Kong study were similar to those used in Frauscher's study; however, their values for EMG activity were still significantly lower than those of previous studies [36,38]. Therefore, we speculate that ethnic variations may be one reason for lower EMG activity in Chinese patients with RBD. Future study is warranted to confirm this observation in Chinese patients and to assess potential clinical implications.

Our data showed that all of the EMG activity including phasic, tonic and phasic + tonic in patients with RBD were higher than in controls. This study also supported Frauscher's suggestion that the mentalis muscle is useful to discriminate patients with RBD from controls [36]. It is notable that the EMG activity of REM sleep in late-onset RBD was higher than in early-onset RBD. This result was consistent with the finding that there were more movements and sleep behavior during REM sleep in the late-onset group. Moreover, a correlation analysis demonstrated that EMG activity in REM sleep was positively related with age at onset. We suggest that EMG activity and movements during REM sleep are increased with increasing age.

4.5. Follow-up

It has become clear that RBD is not an independent disease. In this study, we found four idiopathic RBD patients (6%) converted into secondary RBD (three PD and one dementia) after a mean interval of 10.6 years from RBD onset and a mean follow-up of 1.5 years. Previous prospective studies reported various conversion risks from idiopathic RBD to neurodegenerative disease: 9% after 4 years of follow-up in Hong Kong [10]; 38% at a mean interval of 3.7 years after the diagnosis of RBD [39] and 65.4% after an average of 13.3 years from RBD onset in Minnesota [40]; 21% after a mean interval of 11 years from the RBD onset and a mean follow-up of 4.6 years in Montreal [41]; and 45% after a median of 5 years of follow-up in Barcelona [21]. Our conversion rate appears to be less than that found in other studies; however, the estimated conversion rate will increase to 20% at 5 years when we multiply 6% by 5/1.5. Clearly, the duration of the follow-up of idiopathic RBD is crucial. The four patients were late-onset RBD, but we could not establish the correlation between conversion ratio and age of onset due to the short follow-up. This is an issue to address in a future study.

5. Conclusion

This study demonstrates that Chinese RBD patients have different characteristics from those previously described as typical for RBD when stratifying the patients into early- and late-onset groups. We found more females, an increased proportion of secondary cases, a stronger association with narcolepsy, and fewer sleep-related movements and less EMG activity during REM sleep in early-onset RBD. Furthermore, we found a positive correlation between EMG activity and age of onset of RBD. The follow-up shows that idiopathic RBD in the late-onset group is more likely to develop neurodegenerative disease. Longitudinal studies are necessary to explore the different clinical features and prognosis according to the onset age.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.020.

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References

[1] American Academy of Sleep Medicine. International calssification of sleep disorders. Diagnostic and coding manual. Westchester, IL: American Academy of, Sleep Medicine; 2005.
[2] Schenck CH, Hurwitz TD, Mahowald MW. REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. J Sleep Res 1993;2:224–31.
[3] Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986;9:293–308.
[4] Gagnon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol 2006;5:424–32.
[5] Kang SH, Yoon IY, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. Sleep 2013;36:1147–52.
[6] Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000;123:331–9.
[7] Sforza E, Krieger J, Petiau C. REM sleep behavior disorder: clinical and physiopathological findings. Sleep Med Rev 1997;1:57–69.
[8] Ju Y-E, Larson-Prior L, Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. Sleep Med 2011;12:278–83.
[9] Zanigni S, Calandra-Buonaura G, Grimaldi D, Cortelli P. REM behaviour disorder and neurodegenerative diseases. Sleep Med 2011;12:S54–8.
[10] Wing YK, Lam SP, Li SX, Yu MW, Fong SY, Tsoh JM, et al. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. J Neurol Neurosurg Psychiatry 2008;79:1415–6.
[11] Chiu HF, Wing YK, Lam LC, Li SW, Lum CM, Leung T, et al. Sleep-related injury in the elderly – an epidemiological study in Hong Kong. Sleep 2000;23:513–7.
[12] Lin FC, Lai C-L, Huang P, Liu C-K, Hsu C-Y. The rapid-eye-movement sleep behavior disorder in Chinese-Taiwanese patients. Psychiatry Clin Neurosci 2009;63:557–62.
[13] Bonakis A, Howard RS, Ebrahim IO, Merritt S, Williams A. REM sleep behaviour disorder (RBD) and its associations in young patients. Sleep Med 2009;10:641–5.
[14] Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Robert Auger R. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. Sleep Med 2009;10:60–5.
[15] Li SX, Wing KX, Lam SP, Zhang J, Yu MW, Ho CK, et al. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). Sleep Med 2010;11:43–8.
[16] American Academy of Sleep Medicine for the scoring of sleep and associated events: rules, terminology and technical specifications. Darien, IL: AASM; 2007.
[17] Zhang J, Lam SP, Ho CK, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? Sleep 2008;31:1179–85.
[18] Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in sleep. Sleep 2002;25:120–38.
[19] Iranzo A, Santamaria J, Vilaseca I, de Osaba MJ. Absence of alterations in serum sex hormone levels in idiopathic REM sleep behavior disorder. Sleep 2007;30:803–6.
[20] Chou KL, Moro-De-Casillas ML, Amick MM, Borek LL, Friedman JH. Testosterone not associated with violent dreams or REM sleep behavior disorder in men with Parkinson's. Mov Disord 2007;22:411–4.
[21] Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Martí MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006;5:572–7.
[22] Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296–300.
[23] Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27:317–21.
[24] Lam SP, Zhang J, Tsoh J, Li SX, Ho CK, Mok V, et al. REM sleep behavior disorder in psychiatric populations. J Clin Psychiatry 2010;71:1101–3.

[25] Wing YK, Li SX, Mok V, Lam SP, Tsoh J, Chan A, et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:470–2.
[26] Lam SP, Li SX, Chan JW, Mok V, Tsoh J, Chan A, et al. Does rapid eye movement sleep behavior disorder exist in psychiatric populations? A clinical and polysomnographic case–control study. Sleep Med 2013;14:788–94.
[27] Huang J, Zhang J, Lam SP, Li SX, Ho CK, Lam V, et al. Amelioration of obstructive sleep apnea in REM sleep behavior disorder: implications for the neuromuscular control of OSA. Sleep 2011;34:909–15.
[28] Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Periodic limb movements in sleep in community-dwelling elderly. Sleep 1991;14:496–500.
[29] Frauscher B, Gschliesser V, Brandauer E, Ulmer H, Peralta CM, Müller J, et al. Video analysis of motor events in REM sleep behavior disorder. Mov Dis 2007;22:1464–70.
[30] Massicotte-Marquez J, Carrier J, Decary A, Mathieu A, Vendette M, Petit D, et al. Slow-wave sleep and delta power in rapid eye movement sleep behavior disorder. Ann Neurol 2005;57:277–82.
[31] Oksenberg A, Radwan H, Arons E, Hoffenbach D, Behroozi B. Rapid eye movement (REM) sleep behavior disorder: a sleep disturbance affecting mainly older men. Isr J Psychiatry Relat Sci 2002;39:28–35.
[32] Iranzo A, Isetta V, Molinuevo JL, Serradell M, Navajas D, Farre R, et al. Electroencephalographic slowing heralds mild cognitive impairment in idiopathic REM sleep behavior disorder. Sleep Med 2010;11:534–9.
[33] Fantini ML, Gagnon JF, Petit D, Rompre S, Decary A, Carrier J, et al. Slowing of electroencephalogram in rapid eye movement sleep behavior disorder. Ann Neurol 2003;53:774–80.
[34] Latreille V, Carrier J, Montplaisir J, Lafortune M, Gagnon JF. Non-rapid eye movement sleep characteristics in idiopathic REM sleep behavior disorder. J Neurol Sci 2011;310:159–62.
[35] Pal PK, Calne S, Samii A, Fleming JA. A review of normal sleep and its disturbances in Parkinson's disease. Parkinsonism Relat Disord 1999;5:1–17.
[36] Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep 2012;35:835–47.
[37] Frauscher B, Ehrmann L, Hogl B. Defining muscle activities for assessment of REM sleep behavior disorder: from a qualitative to a quantitative diagnostic level. Sleep Med 2013;14:729–33.
[38] Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2044–51.
[39] Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 1996;46:388–93.
[40] Schenck CH, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): delayed emergence of Parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and analysis of the minimum and maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003;26(Suppl.):A316 [abstract].
[41] Fantini L, Filipini D, Montplaisir J. Idiopathic REM behavior disorder: a longitudinal study. Mov Disord 2001;16(Suppl. 1):S58–S182.